VA | U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

CLINICIAN GUIDE

Pharmacogenomic (PGx) Testing and Heritable Conditions

? DID YOU KNOW

The current VA pharmacogenomic (PGx) panel tests for genes associated with the following **heritable conditions** in addition to providing information on drug-gene interactions.

- Dihydropyrimidine dehydrogenase (**DPD**) deficiency
- Gilbert's syndrome: uridine diphosphoglucuronate-glucuronosyltransferase 1A1 (***UGT1A1***)
- Glucose-6-phosphate dehydrogenase (**G6PD**) deficiency
- Malignant hyperthermia susceptibility (**MHS**): ryanodine receptor isoform 1 (***RYR1***) and ***CACNA1S***

Inform Veterans that PGx testing may identify certain heritable conditions.

Counsel Veterans:

- ✓ Heritable conditions may be identified incidentally.
- ✓ Further medical testing or referrals to other clinicians may be needed if a heritable condition is identified.
- ✓ Share all PGx test results with non-VA clinicians.
- ✓ Do not change any medications before talking with the health care team.

- The heritable conditions included in the VA PGx panel are **relatively benign**, and individuals with these variants typically lead normal lives.
- A PGx test panel should **not** be ordered for the purpose of diagnosing any heritable conditions. Refer to medical genetics if a diagnosis is needed.

Sample consenting script for testing:

The current VA PGx test gives us information on how your body responds to more than 100 common medicines. Although you might not take one of these medicines now, about 50% of VA patients are prescribed at least one of them at some point. Testing can help your care team make better prescribing decisions to try to improve your treatment and reduce side effects.
It may also identify an increased risk for certain heritable health conditions, and we will let you know if that is the case.

It's a one-time blood test. Results come back in a few weeks and are stored in your medical record. Your VA providers will have access to the results. What questions do you have?

***See page 3** if a PGx test result indicates a heritable condition.*

Educate and coordinate care for Veterans with heritable conditions.

Dihydropyrimidine dehydrogenase (DPD) deficiency

WHAT IS IT?

- **An autosomal recessive condition** caused by variation in the *dihydropyrimidine dehydrogenase (DPYD)* gene which encodes the DPD enzyme.[1,2]
- DPD is responsible for the **breakdown of endogenous molecules** (uracil and thymine) as well as the metabolism of the fluoropyrimidine class of medications.[1-3]
- Variation in DPD enzyme function can lead to **excess uracil and thymine** in the urine, cerebral spinal fluid, and blood. While some with deficiencies are asymptomatic, others experience a wide range of neurological symptoms including epilepsy, intellectual disability, microcephaly, hypertonia, and developmental delays which often start in infancy though may appear at any time.[1,3]
- Severe deficiency with early onset neurological symptoms is **rare** but 2-8% of the population has a DPD deficiency that may lead to life-threatening fluoropyrimidine-induced toxicity.[1,2]

WHAT SHOULD I DO NEXT?

- **Refer to medical genetics** if the patient has questions about familial implications or family planning.
- If the patient is a **poor metabolizer**, refer to neurology for unexplained neurological symptoms.
- Encourage the patient to **share this test result with close family members** so they can discuss genetic testing with their own health care teams.

- Counsel patients to share PGx test results with other health care providers, especially **oncologists.**
- Oncologists may refer to ***Applying Pharmacogenomics (PGx) to Fluoropyrimidine Therapy Clinician Guide*** for more on dose adjustment recommendations.

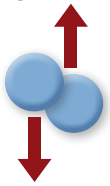
Gilbert's syndrome

WHAT IS IT?

- Gilbert's syndrome is an **autosomal recessive condition** caused by variation in the *UGT1A1* gene which codes for the enzyme that conjugates bilirubin to glucuronic acid for excretion in bile.[4-6]
- Individuals may present asymptomatic, or report episodes of **transient jaundice** resulting from unconjugated hyperbilirubinemia associated with varying enzyme function.[6]
- Jaundice related to Gilbert's syndrome may be triggered by **fasting, febrile illness, physical exertion, dehydration, stress, menses, or certain medications** (e.g., irinotecan, atazanavir).[4,5,7]
- This heritable condition is seen in **3-9%** of certain ancestral groups.[4,6,7]

WHAT SHOULD I DO NEXT?

- If **asymptomatic**, educate on the possibility of jaundice and advise follow up with primary care if episodes occur.
- If **symptomatic** with persistently elevated **total** bilirubin levels, levels > 2mg/dL, or other liver function test abnormalities:
  1. Order conjugated bilirubin and
  2. Refer to GI hepatology for exclusionary diagnosis if clinically indicated.
- Genetics consultation is **not** typically indicated for Gilbert's syndrome due to its relatively benign nature.
- Counsel patients with Gilbert's syndrome to share PGx test results with other health care providers as certain medications, such as irinotecan, may warrant **dose adjustments**.



G6PD (glucose-6-phosphate dehydrogenase) deficiency

WHAT IS IT?

- G6PD deficiency is an **X-linked genetic variation** in the red blood cell (RBC) enzyme G6PD which protects the RBC against oxidative stress.[8]
- Individuals are often asymptomatic but can develop acute hemolytic anemia (AHA) after exposure to certain oxidative stressors such as[8,9]:
  - high-risk medications and dyes (e.g., dapsone, methylene blue, pegloticase, primaquine, rasburicase, tafenoquine, toluidine blue, etc.)
  - foods (e.g., fava beans)
  - infection
  - chemicals (e.g., moth balls)
- Symptoms of AHA include **anemia, jaundice, dark color urine, pallor, fatigue, and abdominal or back pain**.[9-11]
- The degree to which RBCs are impacted by decreased G6PD function varies based on the number of X chromosomes an individual has rather than sex.[8] Therefore, **G6PD enzyme activity must be tested** to classify the degree of severity and inform next steps.
- G6PD deficiency is seen in roughly **5%** of the world's population.[8]

WHAT SHOULD I DO NEXT?

- **Assess if your patient is already aware.** In 1981 the Department of Defense issued Directive 6465.1 requiring G6PD deficiency screening for all personnel entering the Armed Forces and those on active duty not previously tested.[10]
- **If your patient has a prior diagnosis**, review their abnormal G6PD enzyme test result and refer to hematology or medical genetics depending on local practice.
- **If this is a new finding** or no prior enzyme level exists, **order a G6PD enzyme level** to assess severity of deficiency. If found to be deficient by enzyme testing, refer to hematology and/or medical genetics as clinically indicated.
- If confirmed **enzyme deficient**, consider adding the following to the patient's problem list in the medical record: *"glucose-6-phosphate dehydrogenase (G6PD) deficiency, per molecular testing."*
- Provide education to avoid certain high-risk medications, foods, and chemicals previously described.[8,11]

If a PGx test result indicates a heritable condition:

- The ordering provider will be added as a **co-signer** to the PGx results note.
- A **medical genetics consult may help** answer patient questions about heritable conditions and familial implications. See here for VA medical genetics availability (tinyurl.com/VA-medical-genetics) or consider care in the community.
- **The patient will be mailed information** about relevant heritable condition(s) in addition to PGx test results. Samples of this information can be reviewed here: tinyurl.com/PGx-example. Patient education is also available on the Veteran's Health Library: https://www.veteranshealthlibrary.va.gov/Search/142,71762_VA

Malignant hyperthermia susceptibility (MHS)

WHAT IS IT?

- Approximately **70% of individuals with MHS have an autosomal dominant variation** in the *RYR1* gene and 1% have variation in the *CACNA1S* gene, both of which play critical roles in muscle contraction.[12]
- When exposed to a **potent volatile anesthetic** (e.g., sevoflurane, halothane, isoflurane, etc.) or succinylcholine, patients with *RYR1* or *CACNA1S* variants may experience **malignant hyperthermia** (MH) characterized by uncontrolled muscle contractions, possible lethal hypermetabolic reactions, cardiac arrest, and death when not properly treated. Use of these agents in MHS patients is contraindicated.[12,13]
- Patients with MHS are also susceptible to **myopathies** and other inherited muscle disorders, unrelated to medication exposure.[12-14]
- Some patients with MHS may develop MH symptoms with **vigorous exercise, infection, or exposure to extreme heat**.[13,15]

WHAT SHOULD I DO NEXT?

- Refer to neurology for **myopathy assessment.**
- **Refer to medical genetics** for education on the risk of MH, myopathy, and implications for family members and family planning.
- **Counsel on avoiding volatile anesthetics or succinylcholine** and to communicate this finding to other health care providers.
- Counsel to **avoid vigorous exercise in hot environments or when ill.**
- Consider prescribing a **medical alert bracelet.**
- Encourage the patient to **share this test result with close family members** so they can discuss genetic testing with their own health care teams.

PGx Clinical Pharmacist Practitioners (CPPs)

Your PGx CPP may be able to guide you in care coordination for Veterans with heritable conditions. For your PGx CPP contact information, PGx testing availability at your site, and more information about the National Pharmacogenomics Program (NPP), visit the NPP homepage (**tinyurl.com/NPP-site**).

References: 1. Dihydropyrimidine dehydrogenase deficiency. MedlinePlus [Internet]. Updated September 2015. Accessed October 17, 2024. https://medlineplus.gov/genetics/condition/dihydropyrimidine-dehydrogenase-deficiency **2.** Amstutz U, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther.* 2018;103(2):210-216. **3.** Dihydropyrimidine dehydrogenase deficiency. National Center for Advancing Translational Sciences. Updated September 2024. Accessed October 17, 2024. https://rarediseases.info.nih.gov/diseases/19/dihydropyrimidine-dehydrogenase-deficiency **4.** Gammal RS, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. *Clin Pharmacol Ther.* 2016;99(4):363-9. **5.** Vítek L, Tiribelli C. Gilbert's syndrome revisited. *J Hepatol.* 2023;79(4):1049-1055. **6.** Gilbert Syndrome. MedlinePlus [Internet]. Updated February 2012. Accessed October 17, 2024. https://medlineplus.gov/genetics/condition/gilbert-syndrome **7.** Grant LM, et al. Gilbert Syndrome. StatPearls. StatPearls Publishing. 2024, StatPearls Publishing LLC. **8.** Gammal RS, et al. Expanded Clinical Pharmacogenetics Implementation Consortium Guideline for Medication Use in the Context of G6PD Genotype. *Clin Pharmacol Ther.* 2023;113(5):973-985. **9.** G6PD deficiency. MedlinePlus [Internet]. Updated August 2016. Accessed October 17, 2024. https://medlineplus.gov/genetics/condition/glucose-6-phosphate-dehydrogenase-deficiency **10.** Department of Defense Instruction Number 6465.1 (1981). **11.** Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Physician.* 2005;72(7):1277-82. **12.** Gonsalves SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes. *Clin Pharmacol Ther.* 2019;105(6):1338-1344. **13.** Rosenberg H, et al. Malignant Hyperthermia Susceptibility. *GeneReviews* [Internet]. 2003;[updated 2020 Jan 16]. **14.** RYR1 gene ryanodine receptor 1. MedlinePlus [Internet]. Updated May 2020. Accessed October 17, 2024. https://medlineplus.gov/genetics/gene/ryr1 **15.** Ibarra Moreno CA, et al. Myopathic manifestations across the adult lifespan of patients with malignant hyperthermia susceptibility: a narrative review. *Br J Anaesth.* 2024;133(4):759-767.